Applicants note that in the Action, Claim 164 has been included in the rejection. Applicants assume that the inclusion of claim 164 in this rejection was erroneous, as claim 164 has been previously canceled.

B. The Rejection Under 35 U.S.C. §112, Second Paragraph, is Overcome

Claim 98 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, it is asserted that the term "about" in claim 98 is a relative term, which renders the claim indefinite. Applicants respectfully traverse.

The term "about" in a claim does not necessarily render a claim indefinite. For example, in *Ex parte Eastwood*, the term "about" used to define the area of the lower end of a mold as between 25 to about 45% of the mold entrance was held to be clear, but flexible. *Ex parte Eastwood*, 163 USPQ 316 (Bd. App. 1968). Similarly, in *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), the court held that a limitation defining the stretch rate of a plastic as "exceeding about 10% per second" is definite because infringement could clearly be assessed through the use of a stopwatch.

Claim 98 recites "The method of claim 75, wherein the dose of benzimidazole is about 0.1 mg per kg body weight. Based the holding of *Gore v. Garlock*, infringement could clearly be assess through the use of a weighing device such as an analytical balance to measure the weight of a chemical. The Examiner has offered no explanation or

evidence setting forth why this could not be done. Thus, the term "about" in claim 98 does not render the claim indefinite. 721 F.2d 1540.

Therefore, it is respectfully requested that the rejection of claim 98 under 35 U.S.C. §112, second paragraph, should be withdrawn.

C. The Rejections Under 35 U.S.C. § 102(e) are Overcome

1. Nature of the Rejection

Claims 1, 2, 9, 10, 12-22, 29, 75, 76, 83-100 and 161-162 have been rejected under 35 U.S.C. § 102(e) as being anticipated Camden (U.S. Patent 6,262,093) ("Camden"). The Examiner states that Camden anticipates because it teaches (a) a method of inducing apoptosis in cancer cells with abnormal *p53* by administering an effective amount of a benzimidazole derivative, and (b) a method of treating a patient having cancer expressing abnormal *p53* by administering an effective amount of a benzimidazole derivative to induce apoptosis. Applicants respectfully reverse.

2. Camden Fails to Disclose Each Limitation of the Claimed Invention

It is well-established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

a. Claim 1 and Dependent Claims

As to claim 1, and claims dependent therefrom (claims 2, 9, 10, 12-22, 29), Camden fails to anticipate because it fails to expressly or inherently disclose the limitation "wherein the expression of the tumor suppressor gene by the cell and the benzimidazole results in apoptosis of the cell" (claim 1).

The sections of Camden cited by the Examiner do not appear to Applicants to include any information whatsoever regarding the expression of a tumor suppressor gene (*e.g.*, measurement of p53 protein or mRNA), or any information correlating expression of a tumor suppressor gene with apoptosis following administration of a benzimidazole. According to the Action, column 11, line 69 to column 12, line 51 of Camden teaches a method of inducing apoptosis in cancer cells expressing abnormal *p53* by administering an effective amount of a benzimidazole derivative. Applicants find no information in this section of Camden, or any other section of Camden, that would lead one to conclude that ***expression*** of *p53* contributed to apoptosis. The focus of this particular section of Camden is directed to cells expressing ***abnormal*** *p53* (see, *e.g.*, column 12, lines 49-51). Camden does not address whether the abnormal p53 gene was expressed, or whether any expressed *p53* expressed was functional. Further, one cannot infer that expression of *p53* contributed to apoptosis since control cells that lack expression of *p53* were not evaluated in Camden.

Nor is the limitation "wherein the expression of the tumor suppressor gene by the cell and the benzimidazole results in apoptosis of the cell" inherently anticipated. For inherent anticipation to arise "the prior art necessarily functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co.*, 190 F.3d at 1347. (citing *In re King*, 801 F.2d 1324, 11326 (Fed. Cir., 1986); see also *Atlas Powder Co.,* 190 F.3d at 1347-48). For inherent anticipation to arise, there must be, at the very least, expression of a tumor suppressor gene upon apoptotic cell death. Camden does not appear to teach any such a requirement. Indeed, as discussed above, Camden teaches that a normal p53 gene is ***not required*** for apoptosis to occur. Thus, there can be no inherent anticipation.

Therefore, Camden fails to anticipate claim 1 and claims dependent thereon.

b. Claim 75 and Dependent Claims

Camden fails to anticipate claim 75 and dependent claims (*i.e.*, claims 76, 83-100) because Camden fails to expressly or inherently disclose the limitation "wherein the expression of the tumor suppressor gene by the cancer cell and the administration of the benzimidazole results in the inhibition of said cancer" (claims 75). The sections of Camden cited by the Examiner as purportedly teaching this limitation do not include any information pertaining to expression of a tumor suppressor gene, or any information correlating expression of a tumor suppressor gene with inhibition of cancer. The sections of Camden cited by the Examiner (column 12, line 52 to column 13, line 24) appears to Applicants to pertain to evaluation of the benzimidazole derivatives against tumor cells which express abnormal *p53*. Applicants find no information in Camden wherein *p53* protein or mRNA was measured, or any results correlating *p53* expression with inhibition of cancer. Furthermore, as discussed above, Camden presents no information comparing *p53* expressing cells with cells that do not express any *p53*.

Nor is this limitation inherent. Camden fails to disclose, nor are Applicants aware of, any requirement for expression of a tumor suppressor gene upon inhibition of a cancer. Inhibition of a cancer can occur for reasons that are independent of tumor suppressor genes. For example, there may be closure of tumor neovascularization resulting in necrosis, a form of cell death that is distinct from apoptosis. Camden itself discusses necrosis as a separate mechanism of tumor cell death in column 11, lines 66-67.

Therefore, because Camden fails to expressly or inherently disclose the limitation "wherein the expression of the tumor suppressor gene by the cancer cell and the administration of the benzimidazole results in the inhibition of said cancer," there can be no anticipation.

c. Claims 161 and 162

(1) Camden Fails to Disclose the Benzimidazole Structure

Claims 161 and dependent claim 162 are not anticipated by Camden because Camden fails to disclose the structural features of the benzimidazoles set forth in independent claim 161. As set forth in the Amendment, claim 161 has been amended to recite the proviso of "wherein if R^3 is H or chloro, then R^2 cannot be H if R^1 is carbamate." By adding this proviso, Applicants in no way concede that the claims as originally written were anticipated by Camden. Camden fails to disclose the structural features of benzimidazoles set forth in claim 161. As a result, claim 161 and dependent claim 162 are not anticipated.

(2) There is Written Description Support for the Benzimidazole Derivatives Set Forth in Claims 161, 162, and the New Claims

As discussed above, written description support for the structural limitations set forth in amended claim 161, dependent claim 162, and the new claims (183-184), including the added proviso, can be found generally throughout the specification, such as on page 8, line 5 through page 9, line 22.

The Federal Circuit has stated that the test for the written description requirement is "whether the application relied upon 'reasonably conveys to the artisan that the inventor had possession at the time of the later claimed subject matter.'" *In re Daniels*, 144 F.3d 1452, 1456, 46 USPQ2d 1788, 1790 (Fed. Cir. 1998). The section of the

specification on page 8, line 5 through page 9, line 22 clearly conveys possession of benzimidazoles of the structural attributes set forth in claim 161.

Further, to meet the written description requirement, Applicants are not required to explicitly recite the exact language of the proviso in the specification. The Federal Circuit has also noted that "[if] a person or ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, ***even if every nuance of the claims is not explicitly described in the specification***, then the adequate written description requirement is met." *In re Alton*, 76 F.3d 1168, 1175, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). It is respectfully submitted that one of ordinary skill in the art, upon reading the specification, particularly the section cited herein, would have clearly recognized that Applicants contemplated inclusion of benzimidazoles of the structure set forth in amended claim 161 (and dependent claim 162 and new claims 183-184) for inclusion in the method set forth therein. Thus, there is adequate written description for this claim limitation.

c. Additional Limitations Not Disclosed in Camden

(1) "Multidrug Resistant Tumor Cell"

Regarding claims 13, 14, 86 and 87, Camden additionally does not anticipate because it does not disclose the limitation of "wherein the tumor cell is a multidrug resistant tumor cell." It appears to Applicants that Camden only discloses the treatment of cancer with one of the specifically defined benzimidazole derivatives wherein the patient has survived treatment with another anticancer agent prior to treatment with the

benzimidazole compound. This is distinguishable from a tumor cell exhibiting the properties of *multidrug* resistance.

(2) "Wherein the Tumor Suppressor Gene is MDA-7"

Claims 20 and 84 are also not anticipated because Camden fails to disclose any cancer cells expressing the tumor suppressor gene MDA-7. While the Examiner states that all breast cancer cells express MDA-7, this is not the case. It would seem that the Examiner has misinterpreted the information provided in the specification of the present invention (page 14, lines 11-18). The statement is made in reference to Su *et al.*, *Proc. Nat'l Acad. Sci.*, 95:14400-14405, 1998. The reference, entitled, "*The cancer growth suppressor gene mda-7 selectively induces apoptosis in human breast cancer cells and inhibits tumor growth in nude mice*," indicates that ***when breast cancer cells are infected with adenoviral vectors expressing the MDA-7 gene***, the expression of this gene induces apoptosis. Thus, expression of MDA-7 is *not* an inherent property of human breast cancer cells.

d. The New Claims are Not Anticipated by Camden

New claims 183-184 are not anticipated by Camden. Claims 183-184 are dependent claims of independent claims 1 and 75, respectively, and differ from these independent claims by inclusion of the proviso "wherein if R^3 is H or chloro, then R^2 cannot be H if R^1 is carbamate." By adding these new claims, Applicants in no way concede that claims 1 and 75 are anticipated by Camden. For the reasons discussed above, these independent claims are not anticipated by Camden. Written description support for the new claims has been discussed *supra.*. These new claims are additionally

not anticipated by Camden because the structural limitations set forth in the claims are not disclosed in Camden.

e. Conclusion

For the reasons set forth above, Camden fails to expressly or inherently disclose each limitation of claims 1, 2, 9, 10, 12-22, 29, 75, 76, 83-100 and 161-162. Therefore, because Camden fails to anticipate these claims, it is respectfully requested that the rejection of these claims under 35 U.S.C. § 102(e) should be withdrawn.

2. Camden is not Prior Art Because Applicants Have Demonstrated Reduction to Practice of the Claimed Invention Before the Priority Date of Camden

Even if the Examiner alleges that Camden anticipates the claimed invention, such as allegation would be impermissible in view of the fact that the present inventors reduced to practice the claimed invention prior to March 9, 1999, the priority date of Camden. Applicants are in the process of finalizing a declaration under 37 C.F.R. §1.131 to show reduction to practice of the claimed invention prior to March 9, 1999. Submission of this declaration with the present response to the Office Action is slightly delayed due to the fact that one of the inventors is presently residing in India. Applicants plan to file this declaration in a Supplemental Response to the Office Action as soon as this declaration has been executed.

The declaration (Appendix A) demonstrates reduction to practice of the claimed invention prior to March 9, 1999, the priority date of Camden. In accordance with the requirement of 37 C.F.R. § 1.131(b), Applicants have provided in their declaration a

showing of facts of such character and weight as to establish reduction to practice prior to March 9, 1999.

Submitted as evidence of reduction to practice are two Exhibits (Exhibit 1 and Exhibit 2 of the declaration) setting forth experiments and results conducted prior to March 9, 1999. Exhibit 2 of the declaration sets forth findings that treatment of *p53* wild type lung cancer cells with fenbendazole inhibits growth. Declaration, paragraph 6 and Exhibit 2. The study evaluated growth of lung cancer cells or normal lung epithelium (NHBEC) after treatment with fenbendazole (labeled FEN in Exhibit 2) and other agents. Both H1299 and H322 are *p53* deficient NSCLC cells and show modest growth inhibition by fenbendazole after 5-7 days of treatment. Declaration, paragraph 6 and Exhibit 2. In contrast, the *p53* wild type cells A549 and H460 show dramatic inhibition of cell growth by fenbendazole that is evident by day 1-3 and 50-80% growth inhibition by day 5-7 of treatment. Declaration, paragraph 6 and Exhibit 2. The control normal cells, NHBEX do not show growth inhibition by fenbendazole. Declaration, paragraph 6 and Exhibit 2. The results of this study were generated prior to March 9, 1999, the priority date of Camden.

Additionally, Exhibit 1 of the declaration sets forth results of experiments demonstrating reduction to practice of the claimed invention before the priority date of Camden. Reduction to practice is evidenced by a copy of a FACS assay setting forth results of a cell cycle analysis involving A549 (*p53* wild type) non-small cell lung cancer (NSCLC) cells treated with fenbendazole (A549 7EN) or untreated control cells (A549C). Declaration, paragraph 3, 5 and Exhibit 1. The A549C cells show a standard profile of G1/S/G2 cells, indicating a dominant G1 population. Declaration, paragraph 5

and Exhibit 1. The fenbendazole treated cells show a depression of both G2 and S-phases and a G1 block. Declaration, paragraph 5 and Exhibit 1. Furthermore, the fenbendazole treated cells show a distinct sub-G0-G1 population indicative of apoptotic cells. Declaration, paragraph 5 and Exhibit 1.

Thus, the declaration set forth herein demonstrates reduction to practice of the claimed invention because it sets forth findings showing that administration of a benzimidazole to a cell expressing a tumor suppressor gene results in apoptosis. Furthermore, as to claim 1 (and claims dependent therefrom), the findings set forth reduction to practice that expression of the tumor suppressor gene by the cell and the benzimidazole results in apoptosis of the cell by the finding that apoptosis was dramatically greater in cells expressing wild-type *p53* than in cells that are *p53*-deficient.

Furthermore, as to claim 75 and claim 161 (and claims dependent therefrom), which are directed to methods of treating a patient, reduction to practice is further shown by the fact that the cell types used in the experiments conducted by the inventors (*i.e.*, human lung cancer cell lines A549, H1299, H322 cells, and H460) were human cells. Thus, it is submitted that the present Applicants carried out in the United States studies that demonstrate the reduction to practice of the claimed invention prior to the March 9, 1999, priority date of Camden.

Applicants also point out that the law is clear that a Rule 131 declaration need only show so much as the prior art discloses. See, *e.g.*, *In re Stempel*, 113 U.S.P.Q. 77 (CCPA 1957). Without conceding that Applicants have not set forth sufficient information to demonstrate reduction to practice, it is submitted that Camden has

nevertheless been antedated inasmuch as the Rule 131 showing is at least commensurate in scope with that found in Camden.

3. Conclusion

For each of the reasons set forth above, Applicants respectfully request that the rejection of claims 1, 2, 9, 10, 12-22, 29, 75, 76, 83-100 and 161-162 under 35 U.S.C. § 102(e) should be withdrawn.

C. The Rejections Under 35 U.S.C. § 103(a) are Overcome

1. Claims Are Not Obvious Over Camden in Combination with Perdomo

Claims 1-2, 9-10, 12-29, 75-76, 83-106 and 161-162, are rejected under 35 U.S.C. §103(a) as being unpatentable over Camden in combination with Perdomo *et al.* (*J. Cancer Res. Clin. Oncol.*, 124:10-18, 1998). The teachings of Camden are discussed in the previous section. Perdomo is said to teach that determining the *p53* status could make it possible to predict the response to therapy in certain patients, and that the response to cisplatin *in vivo* of NSCLC tumor lines was dependent on *p53* status. According to the Examiner, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references of Camden and Perdomo to achieve the claims of the present invention. Applicants respectfully traverse.

In rejecting claims under 35 U.S.C. §103, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) the prior art reference (or references

when combined) must teach or suggest all the claim limitations; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (3) there must be a reasonable expectation of success. *Manual of Patent Examining Procedure* § 2142. See also *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991). It is important to note that all three elements must be shown to establish a *prima facie* case of obviousness. Thus, if one element is missing, a *prima facie* case of obviousness does not exist.

A *prima facie* case of obviousness has not been established because the prior art references cited by the Examiner do not teach or suggest all of the claim limitations. In particular, for the reasons discussed above, the discussion of which is herein incorporated into this section, the Examiner has not shown that Camden teaches or suggests induction of apoptosis in a cell as the result of expression of a tumor suppressor gene and the administration of a benzimidazole, or inhibition of cancer as the result of expression of a tumor suppressor gene and the administration of a benzimidazole, as found in claims 1, 2, 9-10, 12-29, 75-76 and 83-100. Additionally, Camden does not appear to teach the particular benzimidazoles found in claims 161-162, and new claims. Regarding claims 13, 14, 86 and 87, Camden additionally does not teach or suggest the limitation of "wherein the tumor cell is a multidrug resistant tumor cell."

In addition, as discussed above, the discussion of which is herein incorporated into this section, Camden is not available as prior art because Applicants have submitted a declaration under 37 C.F.R. §1.131 demonstrating reduction to practice of the claimed invention prior to the priority date of Camden.

Furthermore, Perdomo does not teach or suggest the missing limitations that are not disclosed in Camden. The Examiner has not shown where Perdomo includes any information pertaining to benzimidazoles, or the effect of benzimidazoles on tumor cells, nor do Applicants find any such disclosure in Perdomo. Thus, Perdomo fails to provide the missing limitations not taught or suggested by Camden. Further, Perdomo provides no motivation to one of ordinary skill in the art to provide the limitations since it does not even address benzimidazoles. As a result, the Examiner has not met his burden of establishing a *prima facie* case of obviousness.

2. Claims Are Not Obvious Over Camden in Combination with Delatour

Claims 1-3, 9-10, 12-29, 75-77, 83-99 and 161-162, are rejected under 35 U.S.C. §103(a) as being unpatentable over Camden in combination with Delatour *et al.* (*Therapie*, 31:505-515, 1976). The teachings of Camden have been discussed *supra*. Delatour is said to teach the embryotoxic and antimitotic properties of benzimidazole compounds. Specifically, the Examiner states that Delatour *et al.* discloses that mebendazole inhibited tumor growth and increased survival time in mice with Ehrich carcinoma. According to the Examiner, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include mebendazole as taught by Delatour in the method taught by Camden. Furthermore, according to the Examiner, one of ordinary skill in the art would have a reasonable expectation of success in using mebendazole as taught by Delatour in the method taught by Camden. The Examiner also contends that the addition of mebendazole to the method taught by Camden would allow one of ordinary skill in the art to achieve an additional

benzimidazole derivative that induces apoptosis in cells and tumors expressing abnormal *p53*. Applicants respectfully traverse.

A *prima facie* case of obviousness has not been established by the Examiner because the prior art references cited by the Examiner do not teach or suggest all of the claim limitations. In particular, for the reasons discussed above, the discussion of which is herein incorporated into this section, the Examiner has not shown that Camden teaches or suggests induction of apoptosis in a cell as the result of expression of a tumor suppressor gene and the administration of a benzimidazole, or inhibition of cancer as the result of expression of a tumor suppressor gene and the administration of a benzimidazole, as found in claims 1, 2, 9-10, 12-29, 75-76 and 83-100. Regarding claims 13, 14, 86 and 87, Camden additionally does not teach or suggest the limitation of "wherein the tumor cell is a multidrug resistant tumor cell." Additionally, Camden does not appear to teach the particular benzimidazoles found in claims 161-162, and new claims.

Furthermore, as discussed above, the discussion of which is herein incorporated into this section, Camden is not available as prior art because Applicants have submitted a declaration under 37 C.F.R. §1.131 demonstrating reduction to practice of the claimed invention prior to the priority date of Camden.

Furthermore, Delatour does not teach or suggest the missing limitations that are not disclosed in Camden. Delatour includes no information pertaining to induction of apoptosis as a result of administration of a benzimidazole and expression of a tumor suppressor gene. Nor does Delatour include any information pertaining to inhibition of cancer as a result of expression of a tumor suppressor and administration of a

benzimidazole. As a result, the Examiner has not met his burden of establishing *a prima facie* case of obviousness.

D. Conclusion

It is submitted that in light of the foregoing amendments, declaration, and remarks, the invention embraced by the pending claims as been shown to be patentable, and favorable reconsideration is earnestly solicited. Therefore, Applicants respectfully request that the Examiner withdraw each of the above rejections.

III. PETITION FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. § 1.136(a), Applicants petition for an extension of time of one month to and including July 18, 2005, in which to respond to the Office Action dated June 28, 2004. Pursuant to 37 C.F.R. § 1.17, a check in the amount of $60.00 is enclosed, which is the process fee for a one-month extension of time. If the check is inadvertently omitted, or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included herein, the Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski Deposit Account No. 50-1212/INRP:095US.

The Examiner is invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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